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# The Neural Basis of Anxiety Across Menstrual Cycle

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**Abstract:** The effects of estrogen on anxiety-like behaviors results are controversial. Menstrual cycle phase modulates anxiety-related neural function in women have not been sufficiently investigated. The neural base of anxiety possible incongruent across menstrual cycle was investigated in the current study. We studied the neural correlates of anxiety across menstrual cycle approach from cortical evoked magnetic field (MEF) activity under threaten cue stimulus by sLORETA in 14 healthy women. Evaluations included comparisons of the time-course, early vs. late processing (EP: 1-250ms; LP: 251-500ms after stimulus onset) during the menstrual (MC) and peri-ovulatory (OV) phases (MC vs. OV), using dynamic spatio-temporal analysis. Healthy women exhibited dissimilar anxiety-associated patterns of fear neuronal circuitry across menstrual cycle. Analyses revealed significant interaction of the time-course (EP vs. LP) and menstrual cycle phase (MC vs. OV) in the highest anxiety-associated regions. Inversely relation of the anxiety state and insular activation was revealed in the MC vs. OV phase. Results indicated that women can use different attention/cognitive resources in response to fear event across the menstrual cycle. This study presents the first evidence that menstrual cycle phase can modulates anxiety-related neural activation in women. Inconsistent anxiety subtypes may occur at different menstrual cycle. These features are an important consideration in understanding the effect of the menstrual cycle on the neural substrates of anxiety, and provide a potential contribute in pathophysiological or therapeutic implications for menstrual cycle-sensitive psychiatric conditions.

**Keywords:** Menstrual Cycle, Anxiety, Brain, Go/NoGo

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## 1. Introduction

### 1.1. Anxiety in the Menstrual Cycle

Sex steroids play a key role in the regulation of anxiety and fear. However, the menstrual cycle phase modulates the anxiety-related neural activity in women has not investigated. The effects of estrogen on the anxiety-like behaviors results are controversial. Estradiol decreases anxiety behavior and enhance performance in some cognitive tasks [1-3]. Contrary, excessive estrogen can be produce agitation, irritability and enhances anxiety manifestations as inhibitory avoidance has also document [4-8]. Both hypo- and hyper-estrogenism

connect the anxiety related behavior may trace a possibility, that the scenery of anxiety is not a monolithic construct while often overlook manipulated in those hormonal studies. Our observation that the characteristics of anxiety may differ with hormonal status, as well the anxiety provokes hemisphere asymmetry, presenting a resilient affective style across menstrual cycle [9]. Anxiety has specific effects on cognition [10], diverse emotions induced quite different patterns of cognitive processing [9, 11] as well the contrasting pattern of brain activity in distinct of anxiety subtypes has report [12]. The present study as extend our previous sensory level analysis [9], evaluating the anxiety associated cortical response to fear cue stimulus at different menstrual cycle. It is

the first step and preliminary to clarify the neural base of anxiety possible incongruent across menstrual cycle.

### 1.2. Threat-Related Attention Bias in Anxious

Converging evidence has suggested that the attention system of anxious people is particularly sensitive to fear-relevant stimuli [13-15]. Brain attention system is functional segregated by various anxiety in response to threatening cues. Studies have described that exhibiting the ‘vigilance’ or ‘avoidance’ pattern (capture vs. hold bias) to threaten cues in various anxiety disorders [16]. Typically, a characterized effect of anxiety on cognition is specific increased attention capture by threat-related stimuli [10, 17]. Conversely, fear avoidance or rapid disengagement of attention from negative words demonstrated in social anxiety or panic disorder [18-21]. The different aspects of selective attention in anxiety have yet to be fully elucidated [14, 22].

### 1.3. Neural Basis of Anxiety

Neuroimaging studies have demonstrated that brain areas involved in fear circuitry include the hippocampus, amygdala, cingulate, prefrontal and parietal cortex, insula and visual association cortex. Altered insular sensitivity has identified in several clinical populations of anxiety disorders [23]. Converging evidences have suggested that parietal-visual cortical association in the attention system is particularly sensitive to threat cues in anxious people [24, 25]. The parietal cortex plays a critical role in visuospatial processing in response to threats [26, 27], with hemispheric functional lateralization particularly relating to attention selection [28, 29]. The right vs. left posterior parietal cortex (PPC) was associated with the capacity of attention selection bias that relates toward vs. away from salient stimuli had report [29, 30]. rTMS to the right posterior parietal cortex (PPC) disrupted the guidance of attention toward salient stimuli, whereas rTMS to the left PPC affected the ability to bias selection away from salient stimuli [29, 30]. Neuroimage studies have indicated that the anxious apprehension involves more left- than right-frontal activity and that anxious arousal is associated with more right- than left- hemisphere activity [12, 31, 32]. Despite the anxiety take in sensitivity to the attention cue, while has not adequately investigated on the effects specified with menstrual cycle.

### 1.4. Dynamic Spatio-temporal Analysis

The neural network of visual processing is distributed and dynamic. The ERP relies on the assumption of similarity in the activity of interest across trials of the averaging procedure. Previous EEG/MEG studies have implemented wide-ranging time-course analyses [33, 34]. The visual ERP presumes that the time-course of two psychological processes involved in behavioral representations, generally separate as perception vs. cognition, tend to occur in early vs. late processing (EP vs. LP). Generators of the two compare domains lie close to the brain occipital-parietal cortex vs. frontal region, separately. Fear facial NoGo stimulus evokes biological stress responses [35],

and adequacy used to elicit negative emotion compared with passively viewing simple unpleasant pictures.

We investigate the neural base of anxiety with menstrual cycle approach by threaten cue challenge due to the fear signal adequate in understanding the physiological and behavioral characteristics of anxiety [32, 36, 37]. Serum estradiol surges significantly during the ovulatory phase [38-40] and reduces at menstruation phase. Evaluations of the anxiety covariates brain activity was included comparing with the time-course, early vs. late processing (EP: 1-250ms; LP: 251-500ms after stimulus onset), and different menstrual cycle, menstruation vs. periovulatory phases (MC vs. OV) by using the standardized low-resolution brain electromagnetic tomography analysis (sLORETA).

## 2. Materials and Methods

### 2.1. Participants

Fourteen right-handed, healthy young women with regular menstrual cycles (24–35 days) were recruited. The sample had an age range of 18 to 35 years. Participants did not use oral/hormonal contraceptives and were not pregnant. The exclusion criteria included (1) a history of neurological or psychiatric disorders or (2) premenstrual syndrome ruled out by the DSM-IV criteria [41]. The subjects were prevented from using caffeine/tobacco for 12 hours, and alcohol for 48 hours before the study. This study was approved by the Institutional Ethics Committee of Taipei Veterans General Hospital. Written informed consent was obtained from each participant prior to starting the study.

### 2.2. Procedure

Each participant underwent two MEG sessions during the menstrual cycle: in the menstrual phase (MC, from the second to the fourth day after menstrual onset) and in the periovulatory phase (OV, from the twelfth to sixteenth day after menstrual onset) as confirmed by the urinary luteinizing hormone (LH) test. The 306-channel MEG system (Vectoview@, Neuromag, Finland) was exploited to measure the brain neuromagnetic activity. The MEG study was conducted within 36 hours of the LH surge, as detected previously [9]. A repeated measurement, counterbalanced design was used to eliminate any ordering effect: 50% of participants were studied in the MC phase, and the other 50% were studied first in the OV phase. Each participant completed two measurement sessions within two monthly cycles. Anxiety inventory measurements were assessed following each MEG recording.

#### 2.2.1. Stimuli

Participants were required to complete a fear Go/NoGo task. They either responded to a particular emotional facial expression (neutral, sad, happy; Go trials) or were prohibited from responding to a fearful expression (NoGo trials). The stimuli were digitized black and white faces taken from the Ekman collection of faces [42]. Participants saw an image of a

fixed cross for 500 ms, as a warning signal, followed 1000 ms later by an image of a facial expression for 400 ms. To discern possible confound contribution from other cognitive component, e.g., executive control, as commonly involved in a Go/NoGo task, subjects also performed an emotionally neutral Go/NoGo task in a different experimental session on the same day. The participant should respond to a symbol set (square, star and triangle; Go trials) but prohibit the response to a circle symbol (NoGo trials). We used the symbol Go/NoGo task as the neutral control instead of using neutral face as the NoGo event since the neutral face could be recognized as of negative valence and may further complicate the experimental situation [43, 44]. Pictures (or symbols) were sequentially presented on a white background in the middle of a screen in front of the participant. At least 30 successful NoGo trials were completed for each task (fear and neutral). Participants used the right index finger for the Go response. The frequency ratio of the Go/NoGo trials was 80% to 20%. The sLORETA procedure was utilized for the successful NoGo trials (fear and neutral).

### 2.2.2. MEG Recording

An anatomical MRI of each participant was acquired. The T1-weight, 3D gradient-echo anatomical MRI was performed on a 3T MR scanner (Bruker, Germany). The matrix size was set to  $256 \times 256 \times 128 \text{ mm}^3$ , and the FOV was  $230 \times 230 \times 192 \text{ mm}^3$ . Before scanning, the magnetic field shimming was performed automatically, and tri-pilot images were used to adjust the FOV location. Participants were asked to relax and not to move during the scanning procedure.

Participants sat comfortably in a magnetically shielded room. Brain signals were recorded using a whole-head 306-channel neuromagneto-meter (Vectoview, Elekta Neuromag, Helsinki, Finland), digitized at 1024 Hz using a 0.03 to 330 Hz band pass filter. Vertical and horizontal electrooculograms were monitored to reject epochs that coincided with blinks and excessive eye movements, with an amplitude cutoff of 600 mV. Four head-position-indicator (HPI) coils were attached to each participant's head and were used to ensure that no large head movements occurred throughout the measurement period by comparing the positions of these HPI coils before and after the recordings. To ensure that the different measurements covered the same cortical regions of each participant, three predefined anatomical landmarks (the nasion and bilateral preauricular points) were used to confirm that head positions relative to the sensor array were similar across sessions [45]. The analyzed epoch was from 200 ms prior to the onset of the stimulus to 1,000 ms after the onset of the stimulus.

### 2.2.3. Behavioral Assessment

Each participant was requested to complete a State-Trait Anxiety Inventory (STAI) after each MEG measurement, to obtain an index of negative mood. State anxiety (SAI) reflects a transitory emotional state or condition of the human organism [46]. SAI scores were assessed for all participants in the OV and MC phases, respectively. Each of the 20 SAI items was given a weighted score from 1 to 4, with a rating of 4 indicating the

highest level of anxiety. Total score ranged from 20 to 80.

## 2.3. Data Analysis

### 2.3.1. Current Density Reconstruction

Before implementation of a spatial filtering technique, sLORETA, individual high resolution white matter MRI were conducted. The Brain Extraction Tool (BET tool; part of FSL-FMRIB's Software Library) was used to segment the anatomical MRI, removing the skull and dura from MR images.

Brain activity was reconstructed using Curry 5.0. (Compumedics Ltd., USA) and a spatial filtering technique, sLORETA (standardized low-resolution electromagnetic tomography) was utilized in successful NoGo trials- MEG tomographic analysis. sLORETA as provides a reliable and detailed assessments for quantitative analysis in MEG. The single-dipole model may be insufficient to explain cortical neuromagnetic activity because such activity can have multiple sources. The sLORETA conductor model was used in the current density reconstruction (CDR), and in a modified Minimum Norm Least Squares (MNLS, L2 Norm) approach, calculating the current strength for each location by dividing by its error bar (or the length). The sLORETA is an effective CDR method for resolving the MEG inverse problem. In this study, components of the mean global field power (MGFP) were selected carefully from the evoked related fields (ERF) in response to the fear NoGo stimuli. ERF and MGFP peak analyses were performed across the time window from 1 to 500 ms following the onset of the stimulus. The coordinates of each channel were transformed through the MRI-MEG integration system. The offline averaged MEG signals were filtered using a 5-30 Hz band pass filter.

All CDR images were spatially normalized into a standard stereotaxic space using Statistical Parametric Mapping (SPM2; Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, UCL, London, UK), and then a 12mm Gaussian kernel was used for smoothing for statistical analysis. SPM used the standard brain template developed at the Montreal Neurological Institute (MNI), and the coordinates obtained by SPM were convertible into standard Talairach space.

### 2.3.2. Statistical Analysis

Individual statistical maps of the MGFP were computed for successful NoGo trials in each task (fear and neutral), using the general linear model approach. Two major time windows after stimulus onset: 1 to 250 ms, 251 to 500 ms was identified early processing (EP) and late processing (LP) by our previous observations [9]. Second-level (group) analysis as random effects model was conducted for statistical group comparisons (MC vs. OV; EP vs. LP). Correlation analysis with an uncorrected threshold  $p$  of 0.001 (spatial extent threshold = 20 voxels) was implemented to elucidate the covariate region of anxiety in MC and OV. The highest ( $r_s$ ) correlated region of anxiety score (HCR) in each session (four conditions of MC-EP, MC-LP, OV-EP, OV-LP) as voxel-of-interest (VOI) were selected. Of the four activate regions, was used for clarified the interaction effects of the time-course (EP vs. LP) and menstrual phase (MC vs. OV).

A two-way repeated measurements of analysis of variance (ANOVA) on HCR was conducted to determine the interaction effect of time-course and menstrual phase using SPSS-12 (SPSS Inc, USA). Pearson correlation was subsequently applied to elucidate the interaction effect in the four HCR regions. The other selected VOI were in the right insula (R Ins) where the HCR was found in OV-LP, because which region plays a key role in anxiety [23]. The VOI of R Ins was extracted with a 6 mm sphere centering on the region, further allowing phase (MC vs. OV) comparisons. The variance of the behavior data (SAI) and VOI/R Ins for different groups (MC vs. OV) was examined using a paired t-test. The threshold for significance was  $p = .05$ .

### 3. Results

#### 3.1. Image Results

##### 3.1.1. Brain Activity Modulated by Anxiety in the MC vs. OV Group

Table 1 shows the neural correlates of anxiety during

*Table 1. Significant covariates with anxiety score for MC and OV group during fear NoGo.*

Cortical region	BA	Coordinate			Voxel level	
		x	y	z	Z max	p
MC_EC						
R Precentral G	6	32	-12	69	3.32	<0.001
R Precentral G	4	36	-29	71	3.06	0.001
R Sup Parietal L	7	20	-63	62	3	0.001
L Sup Frontal G	6	-8	0	68	2.96	0.002
L Sup Frontal G	6	-4	15	64	2.67	0.004
R Sup Frontal G	6	6	23	62	1.7	0.045
L Postcentral G	7	-8	-55	71	2.87	0.002
L Precuneus	7	-12	-79	56	2.2	0.014
L Superior Parietal L	7	-44	-65	51	2.3	0.011
R Occipital Cuneus	19	24	-93	40	2.13	0.016
R Occipital Cuneus	19	16	-93	42	1.82	0.034
OV_EC						
L Parietal Postcen G	3	-49	-15	54	3.2	0.001
L Precentral G	6	-44	0	46	3.14	0.001
L Inf Parietal L	40	-40	-36	52	2.01	0.022
R Mid Frontal G	6	40	-1	61	2.77	0.003
L Inf Parietal L	40	-57	-50	56	2.38	0.009
R Mid Occipital G	19	59	-68	-3	1.96	0.025
R Mid Occipital G	19	55	-78	-6	1.74	0.041
R Mid Temporal G	21	63	-60	3	1.71	0.044
R Postcentral G		50	-20	58	1.91	0.028
MC_LC						
L Sup Frontal G	6	-14	30	52	3.01	0.001
L Sup Frontal G	6	-8	-4	67	2.96	0.002
L Sup Frontal G	6	-2	23	62	2.91	0.002
L Inf Frontal G	47	-40	29	-5	2.43	0.007
R Precentral G	4	53	-12	39	2.4	0.008
L Sup Temporal G	38	-40	13	-19	1.93	0.027
L Sup Temporal G	38	-49	11	-16	1.84	0.033
OV_LC						
R Sub-lobar, Insula	13	34	-42	17	3.96	<0.001
R Sup Temporal G	13	51	-40	20	3.65	<0.001
R Sup Temporal G	39	51	-53	23	3.54	<0.001
R Inf Frontal G	10	44	49	1	2.43	0.008
R Inf Frontal G		55	31	0		
R Mid Frontal G	46	44	42	24	2.24	0.012
R Precentral G	6	36	-11	58	2	0.023
R Occipital Cuneus	18	12	-97	12	1.97	0.024

different time-courses (EP and LP) and menstrual phases (MC vs. OV) during fear NoGo condition. Anxiety covariates cortical activation for MC-EP, primarily in the right parieto-occipital regions, including the R precentral G, sup parietal L, occipital cuneus, and bilateral sup front oparietal G L. Of the MC-LP, anxiety covariates cortical activation primarily in the left temporal- frontal regions, including the left superior frontal gyrus (SFG) [BA6], inferior frontal gyrus (IFG) [BA47], sup temporal G [BA38], and R precentral G [BA4].

The anxiety covariates cortical activation for OV-EP, primarily in the left posterior parietal regions, including L parietal postcentral G [BA3/6], inf parietal L [BA40], and R mid-occipital-temporal G [BA19/21]. Of the OV-LP, the anxiety score associated with brain activation primarily in the right insula temporal-frontal cortex (rITFC) areas, including R insular [BA13], superior temporal gyrus [BA13/39/38/22], inferior/mid frontal G [BA10/46], precentral G [BA6], and left postcentral gyrus [BA5/7].

Cortical region	BA	Coordinate			Voxel level	
		x	y	z	Z max	p
L Postcentral G	5	-34	-43	67	1.97	0.024
L Sup Parietal L	7	-18	-63	58	1.92	0.028
R Paracentral L	4	8	-36	63	1.91	0.028
R Sup Temporal G	38	55	9	-14	1.91	0.028
R Sup Temporal G	22	61	4	-4	1.85	0.032

All voxels are significant at  $p < 0.05$ , uncorrected for multiple comparisons with extent threshold at 20 voxels; BA: Brodmann Area; Z max report the Z value at the cluster Peak.

**Table 2.** Significant covariates with anxiety state for MC and OV group during Symbol Neutral NoGo.

Cortical region	BA	Coordinate			Voxel level	
		x	y	z	Z max	p
MC_EC						
R Middle Frontal G	10	44	47	14	2.72	0.005
R Middle Frontal G	46	48	43	5	2.34	0.012
R Superior Frontal G	10	36	53	14	2.32	0.012
L Parietal Precuneus G	7	-10	-68	44	2.56	0.007
OV_EC						
R Limbic Parahippo G	36	34	-28	-24	4.07	<0.001
R, Temporal, Fusiform G	20	44	-32	-25	3.88	<0.001
R Parietal Inferior, G	40	59	-47	39	3.66	<0.001
R Superior Frontal G	10	30	52	23	2.54	0.006
R Superior Frontal G	9	34	46	31	2.45	0.007
R, Occi Cuneus, G	18	4	-86	25	2.43	0.008
L Parietal Postcentral G	40	-57	-23	14	2.2	0.014
R Occi Cuneus, G	17	10	-83	4	2.19	0.014
L Occi Lingual G	17	-10	-89	-2	2.08	0.019
L Occ Lingual G	17	-2	-85	3	1.88	0.03
R Mid Occi G	18	28	-93	14	2.18	0.015
R Occi Cuneus	17	20	-91	8	1.95	0.026
L Sup Temporal G	22	-49	-58	14	2.11	0.018
R Sub-lobar, Thalamus, G		10	-21	3	2.09	0.018
R Sub-lobar, Thalamus, G		12	-25	10	1.91	0.028
L Super Frontal G	9	-6	58	32	2.08	0.019
L Medial Frontal G	9	-24	36	18	2.06	0.02
R Middle Occi G	19	50	-73	7	2.04	0.021
R Middle Occi G	19	48	-80	2	1.94	0.026
R Middle Temporal G	39	48	-75	15	1.92	0.027
R Limbic Post Cingulate, G	30	10	-66	11	2.01	0.022
L Limbic Parahippo G	35	-18	-11	-25	1.97	0.024
L Parietal Supramarginal G	40	-51	-49	28	1.96	0.025
L Temporal, Fusiform G	20	-42	-32	-22	1.86	0.031
MC_LC						
R Parietal Postcentral G	2	59	-19	47	2.86	0.002
R Parietal Postcentral G	2	63	-29	42	2.56	0.005
R Frontal Precentral G	6	59	-11	43	2.47	0.007
R Sup Parietal G	7	42	-58	49	2.77	0.003
L Medial Frontal G	6	-4	-14	63	2.37	0.009
R Middle Frontal G	6	38	-1	59	2.26	0.012
R Frontal Precentral	6	46	-7	56	2.08	0.019
R Middle Frontal G	6	40	7	55	1.86	0.032
L Inferior Parietal L	40	-38	-40	50	1.82	0.034
OV_LC						
R Mid Occip G	18	34	-87	15	3.99	<0.001
R Middle OcciG	19	48	-79	15	3.88	<0.001
R Occi Lingual G	17	12	-85	4	3.81	<0.001
L Parietal Postcentral G	40	-38	-32	51	3.63	<0.001
L Temporal G	42	-65	-13	12	3.26	0.001
L Superior Temporal G	42	-65	-25	14	3.2	0.001
R Inferior Frontal G	9	65	9	25	3.51	<0.001
R Mid Frontal G	46	61	24	23	3.11	0.001
R Mid Frontal G	9	51	25	36	3.05	0.001
R Med Frontal G	10	8	47	9	2.36	0.009
R Sub-lobar Lentiform NucleusG		20	12	9	2.07	0.019
R Sub-lobar Lentiform		20	4	-2	1.95	0.025

Cortical region	BA	Coordinate			Voxel level	
		x	y	z	Z max	p
NucleusG						
R Sub-lobar CaudateG		14	17	-8	1.77	0.039
R Frontal Precentral G	4	32	-24	62	1.91	0.028
R Parietal Postcentral G	3	24	-30	66	1.69	0.045

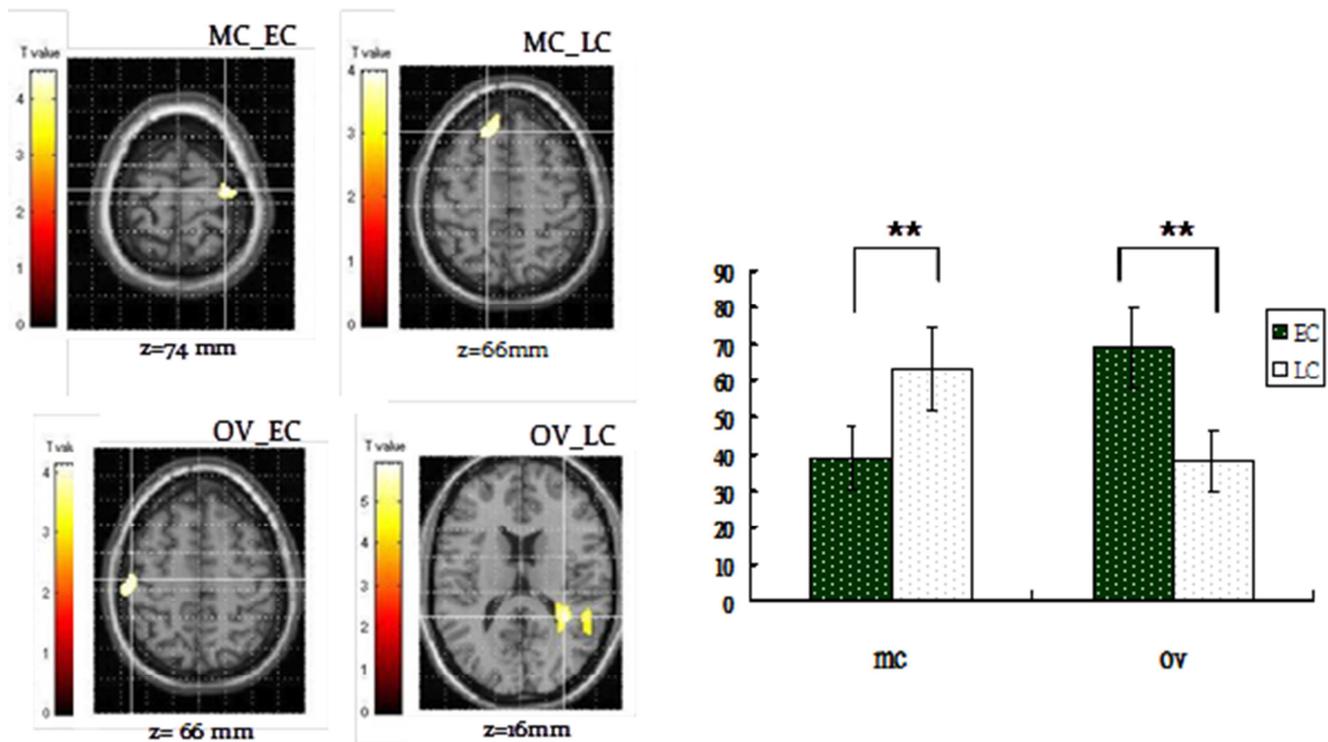
All voxels are significant at  $p < 0.05$ , uncorrected for multiple comparisons with extent threshold at 20 voxels

**3.1.2. Comparing Spatiotemporal Processing for MC vs. OV**

The four HCRs of anxiety- neurocircuit exhibited (MC-EP, MC-LP, OV-EP, OV-LP) a significant interaction for the time-course (EP vs. LP) and menstrual phase (MC vs. OV) [ $F(1, 11) = 33.21; p < .0001$ ]. Significant greater activation in the LP during the MC phase (EP < LP;  $p = .001$ ) and contrary, greater activation in the EP in the OV group (EP > LP;  $p = .002$ ) (Figure 1). It displays that the anxiety covariates discrepancy cognitive resources across menstrual phase. The MC group used more late than early processing, whereas the OV group used more early than late processing in response to fear cues. Comparing different menstrual phase, we found a sub-significant change that the HCR activation of EP greater

in OV, while the activation of LP greater in the MC (EP: MC<OV/  $p = 0.068$ ; LP: MC> OV/  $p = 0.121$ ).

The four HCRs of anxiety- neurocircuit exhibited inverse lateralization patterns (as hemispheric transfer) during different time-courses (EP vs. LP) and menstrual cycles (MC vs. OV) for fear NoGo condition. The pattern of hemispheric transition through the time-course, EP to LP was found the left- then right- hemispheric processing in the MC phase and the right- then left- hemisphere processing refers to the OV phase (Table 1). There was no intra- and inter-hemispheric shift observed in the emotionally neutral NoGo trial from this dynamic covariate analysis (Table 2).

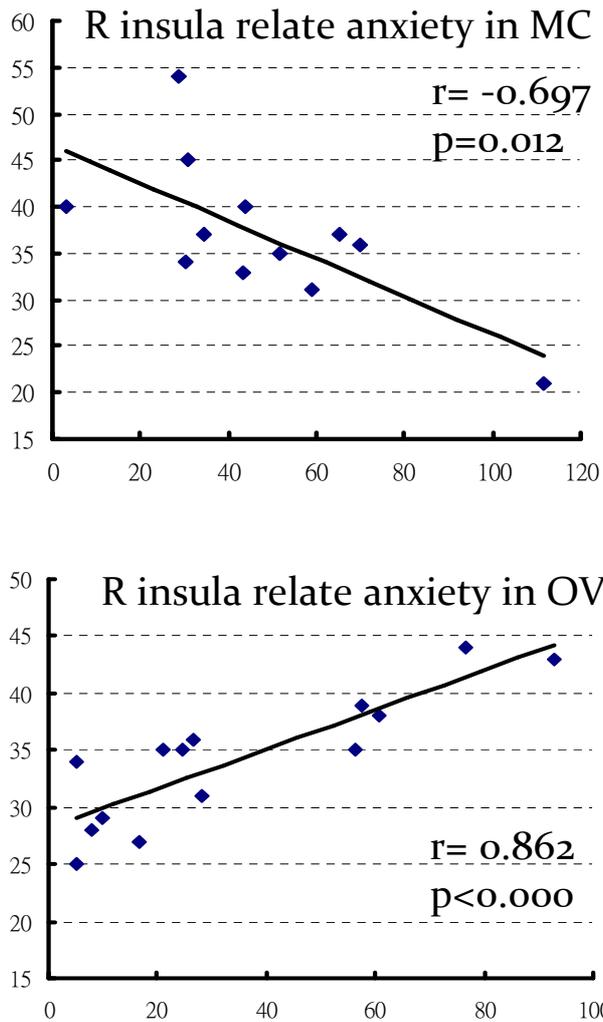


**Figure 1.** Slice display the brain regions correlated with anxiety score at different time course during fear NoGo stimuli across menstrual cycle. The highest correlated areas of anxiety show interhemispheric transfer include: (1) R FPG for MC\_EC; (2) L SFG for MC\_LC; (3) L PPC for OV\_EC; (4) R Insular for OV\_LC. Significant interaction of the time course (EC vs. LC) with menstrual phase (MC vs. OV) was revealed ( $F = 33.21; P < 0.001$ ). The Bar displayed a contrast draft of activation strength in 4 regions: MC: EC < LC; OV: EC > LC (both  $P < 0.005$ ). All voxels are significant at  $p < 0.001$ , uncorrected for multiple comparisons with extent threshold at 20 voxels. L: left; R: right; EC: early component; LC: late component; PPC: posterior parietal cortex. The dynamics hemispheric specialization integrates in the context by the 4 highest anxiety covariate regions was exhibit.

**3.1.3. ROI**

The HCR of the right insula [34,-42, 17] (R Ins) in OV-LP (Table 1) was specific selected for further comparing in MC vs. OV. Inversely relation of the anxiety score and insular was found in fear NoGo condition across menstrual cycle (Figure 2). Significant negative vs. positive relation was occurred in

the MC vs. OV respectively ( $r = -0.697; r = +0.862$ ; both  $p < .05$ ) (Figure 2).



**Figure 2.** The anxiety scores were inversely related to insular [34,-42, 17] across menstrual cycle phase. Significant negative vs. positive relationships exhibited in the MC vs. OV phases, respectively (both  $p < 0.001$ ).

### 3.2. Psychological Assessment

There was no difference in anxiety score (SAI) between the menstrual phases. The SAI mean score  $\pm$  standard deviation (SD) was  $35.8 \pm 8.4$  and  $34.2 \pm 5.7$  during the MC and OV phase, respectively. There was no difference in the error rate between fear facial NoGo trial (17% for MC vs. 18% for OV) and neutral symbol NoGo trial (3% for MC vs. 4% for OV) across the menstrual cycle. The error rate for fear facial NoGo trials did not differ between the menstrual phases (17% for MC vs. 18% for OV).

## 4. Discussion

This study investigates the neural base of anxiety by evaluating cortical evoked magnetic field (MEF) activity in response to fear cues across menstrual cycle. Evaluations of anxiety covariates brain activity included comparisons of the time-course (EP: 1-250ms; LP: 251-500ms after stimulus onset) and different menstrual cycle (MC vs. OV) in a dynamic spatio-temporal analysis. There were two main findings: (1) women show dissimilar anxiety-associated

patterns in neuronal activation of fear circuitry in different menstrual cycle. Significant interaction between the time course (EP vs. LP) and menstrual cycle (MC vs. OV) was revealed in the region of the highest anxiety covariates regions. Inter-hemispheric transfer from the EP to the LP occurred only during the fear NoGo condition; and (2) significant negative vs. positive relationships of the anxiety score and insula activation was exhibited in the MC vs. OV phases, respectively (both  $p < .05$ ; Figure 2). Images and behavioral studies have revealed that the threaten signal as an important role in modulating spatial attention in anxiety [10, 17, 25]. Dynamic transfer of the intra- and inter-hemisphere processing to fear cue implied that women can utilize different attention/cognitive resources in their different menstrual cycle. Different emotions are characterized by distinct patterns in cognitive processing [11], and thus, inconsistent anxiety subtypes may exist in different menstrual cycle phases.

### 4.1. General View

Anxiety-associated patterns in neuronal activation of fear circuitry were dissimilar across the menstrual cycle. Significant interaction between the time-course (EP vs. LP) and menstrual cycle (MC vs. OV) was evident in the four HCRs (highest  $r_s$  correlated region with anxiety score) ( $p < .0005$ ). Anxiety recruited more cognitive (or action) neural substrate in the MC phase, whereas the OV period favored the perception domain (MC: EP  $<$  LP,  $p = .001$ ; OV: EP  $>$  LP,  $p = .002$ ). Estrogen enhances prefrontal-related cognitive function [11], relative lower estrogen is associated with well documented deficits in high-order cognitive processes. High load on „frontal“ cognitive control processes increased may illustrate a compensation mechanism during female MC phase. Females with Turner's syndrome, lacking estrogen due to genetic deficit, could compensate for executive dysfunction via recruitment of additional prefrontal cortex regions involved in inhibition, attention, and working memory for successful performance of Go/NoGo tasks [47]. Conversely, female present significant activation in the perception- neural substrate in OV phase. The perception process reinforcements empirical relates to motivational force. Female may have more perceptive to fear stimuli, warning the organism of possible impending danger in the OV phase. The high perceptual load whereas might provide an optimal condition succeeding for their propagation.

The neural correlates of the anxiety exhibited spatio-temporal dynamic transfer across the menstrual cycle. Interhemispheric transmission throughout the time-course showed marked variations, MC: right to left and OV: left to right during the fear NoGo condition, but not in neutral condition (Table 1, 2). The interhemispheric integration for lateralized cognitive processes was reported by hormone-dependent modulation [48-50]. A powerful neuromodulatory action of estradiol on the dynamics of functional brain organization in the female brain had reported [50]. The LH dominances to the activation regulatory system while the RH device to the arousal regulatory system. It conjectured to determine hemispheric specialization for perception, action,

emotion and cognition [51]. Interaction between the cerebral hemispheres may allow both hemispheres to contribute their processing resources in order to cope efficiently with complex tasks [52]. Dysfunctional hemispheric transformation signature an index of neuropsychiatry ill-health base has demonstrated [29, 53-56]. These features are an important consideration in understanding that the dynamics of neurons or brain areas and how their interactions of anxiety with hormonal modulation are influenced possibility by and shape behavior. Estradiol can modulate functional brain organization [50], results further indicated that the Anxiety as a vigor moderator integrate in the intra- and inter-hemispheric dynamic transformation and regulating intrinsically self organization to fear cue response across menstrual cycle.

## 4.2. Specific View

### 4.2.1. Anxiety Covariates Brain Activity in MC-EP

Anxiety covariates with neural circuitry was primarily in the right hemisphere, including the occipital cuneus [BA19], superior parietal lobe [BA 7], and frontal-cingulate gyrus (FCG) networks [BA4, 6]. The parieto-occipital area (PO) of the right side is known involving basic visual processing. Visual association of the extrastriate cortices [BA 18, 19] was related to anxiety mood modulation and threaten cue detected [28]. Previous studies have shown that responses to danger signals in the visual cortex associated with an adaptation mechanism for rapid discrimination to aversive stimuli [10]. Numerous reports have described the anxiety can be modulating the activation of the right visual-parietal network [10]. Observations of the right posterior parietal cortex (rPPC) [BA7] were specifically relating the behavior of engage attention cue in normal or anxious participants [10]. Results indicate that the anxiety engaged relative sensitivity on the part of the visual-parietal network of right hemispheric functional in danger cue attend/approach [57] to fear cue early processing for MC phase.

### 4.2.2. Anxiety Covariates Brain Activity in MC-LP

Anxiety associated with neuron activation was primarily in the left hemisphere, including the SFG [BA6] and part of the dorsal lateral prefrontal cortex (dlPFC), during MC-LP. Prior research identified left dlPFC activation in the cognitive model of anxiety [10]. This area specializes in attentional-cognitive functions [58] with involvement in the performance of cognitive demands of anxious apprehension [12] in trait-anxious people [17]. Results concerning the left side of the SFC, LSTG and OFG suggest a specific reward bias function [59, 60], particularly in the OFG regions [BA 47], which are associated with inhibitory control processes [61], in which reward value plays a mediating role. Control over fear/stressors is a critical determinant of a person's physical and psychological wellbeing [62], with control of attention and receptiveness to emotionally evocative stimuli is a basic form of emotional regulation [63]. Anxiety in the MC condition involves the reward stream of the OFC, which may reveal a natural require for mediating subjective hedonic experience [64].

### 4.2.3. Anxiety Covariates Brain Activity in OV-EP

The neural components of anxiety in the OV phase was included the left PPC and parietal-temporal regions (Table 1). The left PPC has an important role in ignoring danger or grasping action in response to an attentional cue [29, 65]. Serial TMS and neuroimaging studies support that the bilateral PPC has opposite bias in the selection or suppression of saliency. The right vs. left PPC was associated with toward vs. away salient stimuli, as described [29, 30]. In previous studies, activation of the left intraparietal sulcus (IPS; BA40) associated with motor attention [66-68] and visually guided grasping [69, 70] in response to salient stimuli. The IPCC system is involved in saliency cue suppression, with relevance to the neuropsychological findings that several anxiety disorders exhibit hold or disengage components of visual attention. Studies have described patients with anxiety and phobia as displaying fear avoidance of threat-related expressions [14, 16, 22], and showing behavioral inhibition or freezing [71, 72]. The administration of estrogen can enhance freeze-avoidance responses to danger cues in ovariectomized mice [7]. Cortical activation of the IPCC network which covarying with anxiety score in OV-EP, might provide rapid protection against potential harm and contribute in propagation for the species.

### 4.2.4. Anxiety Covariates Brain Activity in OV-LP

Significant anxiety correlated brain regions were turning to the right insular temporal-frontal cortex (rITFC) areas in OV-LP (Table 1). The rITFC network is involved in the dorsal attention system, and related hypervigilance, sensitivity to anxious arousal [12], panic, phobias, and non-remarkable anxiety ratings in participants [23]. Functional neuroimaging or lesion studies have reported that the brain activation of anxious arousal specifically occurring in the right side, including the dlPFC, vlPFC, and vmPFC [73-79]. HRT can enhance activation of the right hemispheric vigilance system in postmenopausal women [80]. Estrogenic effects on fear and arousal status mostly arise in the limbic-amygdala structures [8], which reciprocally connect to the lateral intraparietal area (LIP) [BA 7], and critically support avoidance-related behaviors. Prior researches have suggested that the right insula has an important role in the anticipation of affective processing during aversive images, and that anticipation of future harm is a key aspect of anxiety [81, 82]. The right inferior PFC (rIPFC), which forms part of the vlPFC, specializes in inhibition of negative emotions or inappropriate motor responses [83-86]. Regions may afford a capacity for obliterate the left PPC create in EC, may well neutralize ongoing withdraw responses reinforcement, outlines a possible that minimize the potential of social rejection and maintain safety behaviors in the OV phase

## 4.3. ROI: Relationship Among Anxiety and Insula Activation

We also confirmed in our brain regions of interest significant relationships with anxiety score and the posterior insula, which reversed directions as significant positive vs.

negative correlation disclosed in OV ( $r = +0.862$ ;  $p < .001$ ;) vs. MC phase respectively ( $r = -0.697$ ,  $p < .05$ ) (Figure 2). The region of the insula is critical for cognitive, affective, and interoceptive state processes, and associate with attention property. The posterior insula is involved in the integration of excitatory and inhibitory neurotransmission associated with BDNF, which can regulate stress and anxiety-like behaviors [87, 88]. Altered insular sensitivity has been observed in several clinical anxiety disorders (not all) which hyperactivity as a neuroimage marker of anxiety proneness [23, 82, 89]. Paulus [23] has reviewed that individuals who are prone to anxiety show an altered interoceptive prediction signal, i.e., manifest augmented detection of the difference between the observed and expected body state [81, 82]. Women may have a higher awareness on the internal state of their bodies, thus activate the posterior insula, of engage region attention resources to modulate cognitive responses or behavior in the OV phase.

The right insula plays a major role in diverse cortical functions as well in cardiac autonomic control [90, 91]. It is associated with arousal and sympathoadrenal stress responses and also involved in parasympathetic functions, which engages diverse homeostatic afferents for asymmetrical lateralization in the left and right forebrain had documented [92, 93]. Previous studies reported that estrogen excites neurons of the insula cortex by modulating GABA neurotransmission [94], enhancing its sympatho- excitatory effects [95]. Asymmetric homeostatic afferent activation of the insular and evoke opponent hemispheric processing to anxiety state simultaneously observed in the hormonal modulation, resonance the scenery of anxiety driving diverse in the MC vs. OV. The anxiety score negative relates to insular may account a down-regulating activity of the posterior insula as by relay more left SFC and IFC neuron engagement (Table 1) for possibility varies of perception of the internal body state or emotional regulation during MC phase. Inversely relation of the anxiety state and insular except response to the anxiety motivating incongruent at MC vs. OV, also reverberate the role of the insular in play a diverse functions, linked to emotion or the regulation of the body's homeostasis at different menstrual phase.

#### 4.4. Converge Summary

The neural base of anxiety possible incongruent across menstrual cycle was investigated in the current study. Result disclosed that anxiety associated with dissimilar fear neurocircuitry during different female menstrual phases. Anxiety covariates cortical activation revealed a dynamic intra- and inter-hemisphere interaction in the occipital-parietal-frontal association, that account female can utilize different cognitive resources in response to fear cue across menstrual cycle. Base on the anxiety has specific effects on cognition, different emotions are characterized by distinct patterns in cognitive processing [11, 14]. We claimed that inconsistent anxiety subtypes may occur at different stages of the menstrual cycle. In spite of the author Heller et al. have report that the anxious apprehension involves more left- than

right-frontal activity and that anxious arousal is associated with more right- than left- hemisphere activity [12, 31, 32], the anxious apprehension (e.g., worry) and anxious arousal (e.g., panic) whether mutually exclusive precisely within both phase (MC vs. OV) needs to be tested experimentally in the future. These data may offers an interpreted for the effects of estrus status on anxiety related behaviors have not arrived at a clear consensus, that may originate by ambiguous measure in past hormonal research as of the scenery of anxiety is not a monolithic construct. Our result perspective to the neural basis of anxiety can be modulating by female hormonal cycle, cleverly utilize an identical inventory in dynamic relative comparison analysis. Results suggesting the types of anxiety should be considerate into experimental manipulations in future hormonal research, as well significantly differ in psychological and physical characteristic could present in subtypes of anxiety.

The present findings are tempered by several limitations. First, there are several features of the fear NoGo study could be deliberate, like the result also suitable claimed in an opponent appetitive-aversive neural processes or affect regulatory processes to negative emotional challenge. While the main goal of study address the anxiety-neural base with menstrual cycle modulation in virtue of our previous sensor level report [9]. Hence, findings of hemispheric lateralized in PPC and PFC in each EP vs. LP observed allow us debate those network towards in threat-related responses of cognitive biases, based on attention system of anxious individuals particularly sensitive to the fear event. Second, the results are based on relatively small samples, while study conduct a within-subject comparison design which ameliorate inter-subject variations, thus yield a higher statistical power than that of between-subject comparison experiment [48].

It is known that natural fluctuation of sex hormone levels during the menstrual cycle, i.e. estrogen in particular, can modulate functional cerebral asymmetries and the interhemispheric crosstalk [50]. The self-organization process can be task specific which are dependent on cognitive, emotional and behavioral element as well as biological demand at different menstrual cycle. The effect of the menstrual cycle on the neural substrates of anxiety exhibited dissimilar patterns of fear response across menstrual cycle, optimize for a potential contribute provided in pathophysiological or therapeutic implications for menstrual cycle-sensitive psychiatric conditions.

## 5. Conclusion

The study investigated the possible incongruent of the neural basis of anxiety across menstrual cycle. Dissimilar anxiety-associated patterns of neuronal activation in response to fear stimuli were found at different menstrual phase. Anxiety covariates cortical activation revealed a dynamic intra- and inter-hemisphere interaction in the occipital-parietal-frontal association, account that female can utilize different cognitive resources in response to fear cue across menstrual cycle. This study presents the first evidence that the

menstrual cycle phase can modulates anxiety-related neural activation in women. Inconsistent anxiety subtypes may occur at different menstrual cycle. Future investigation of the precise anxiety subtypes exhibited during different menstrual cycle phases is warranted.

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